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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/678,534	05/24/00	CROSSMAN	MSA-017.02

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MYERS, C	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/578,534	Applicant(s) CROSSMAN ET AL.	
	Examiner Carla Myers	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *8-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 77-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to examine the claims of all groups I-VIII. However, it is maintained that undue burden would be required to examine the claims of groups II-VIII along with the claims of group I as evidenced by the fact that the claims of groups I-VIII have acquired a separate status in the art as recognized by their different classification and as recognized by their divergent subject matter and because a search of the subject matter of invention 1 is not co-extensive with a search of inventions II-VIII. With respect to the restriction between groups I and II, it is maintained that restriction between these two groups is proper because the kits of group II can be utilized in a materially different method, such as general methods for genotyping IL-1 genes.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that claims 77 and 78 are in improper Markush format. See Ex parte Markush, 1925 C.D. 126 and In re Weber, 198 USPQ 334. The methods of claims 16 (group III) and 43 (group V) have been withdrawn from consideration as being drawn to a non-elected invention. Applicants are required to amend the claims to set forth only the elected inventive groups.

2. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. In particular, Applicant is required to amend the specification to indicate that the present application is a continuation-in-part of U.S. application 09/431,352.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). As the sequence disclosures in claims 1-7 and 77-79 are identical to those set forth in 09/431,352, the Sequence Listing from 09/431,352 have been used to examiner claims 1-7 and 77-79. However, in response to this Office action, Applicants must comply with the requirements of 37 CFR 1.821-1.825 as set forth on the attached Notice to Comply with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In particular, Applicant is required to submit a CRF and paper copy of the Sequence Listing containing the disclosed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOS into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

4. The disclosure is objected to because of the following informalities:

In claim 5, line 3, the second recitation of "and 13" should be deleted.

5. Claims 1-7 and 77-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining whether a SVD patient has or is predisposed to developing arterial restenosis wherein the methods comprise detecting the presence of IL-1RN (VNTR) allele 1 as indicative of a predisposition to arterial restenosis in SVD patients, does not reasonably provide enablement for methods for determining whether a subject has or is predisposed to developing restenosis wherein said methods detect any other alleles in the

IL-1 gene cluster, including IL-1A (+4845), ILb (-511) or ILb (+3954), or any alleles in any other non-IL-1 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The specification identifies a number of IL-1 alleles, including IL-1RN(+2018), IL-1RN (VNTR), IL-1A (+4845), ILb (-511) and ILb (+3954). The specification (page 66-67) teaches that the IL-1RN (VNTR) allele 2 is associated with a lower restenosis rate in patients with SVD. Accordingly, the specification has enabled methods for determining whether an SVD patient has or is predisposed to developing restenosis wherein the methods comprise detecting the IL-1RN (VNTR) allele 1 as indicative of an increased likelihood of having or being predisposed to restenosis. However, the specification also teaches that no significant association was found between the occurrence of IL-1RN(VNTR) allele 2 and restenosis in MVD patients (see page 66 and Table I). This finding clearly emphasizes the unpredictability in the art of establishing a correlation between IL-1 alleles and the occurrence of disorders associated with cardiovascular disease in that the results obtained with one type of population (SVD patients) cannot be

extrapolated to other populations (e.g., MVD patients). Accordingly, the specification is not enabling for methods in which restenosis is diagnosed in non-SVD patients, particularly in MVD patients. There is no universal association between the presence of alleles in the IL-1 gene cluster and the occurrence of restenosis. The art has not established a correlation between any alleles of IL-1 and the occurrence of restenosis which would allow for a general relationship to be established between the presence of an IL-1 gene cluster allele and any cardiovascular disease. In addition, the specification has not taught any particular attribute of the IL-1RN (VNTR) allele that could be extrapolated to other alleles in order to predictably identify other alleles in these genes and other IL-1 genes or any other unstated gene which would be predictive of restenosis. The specification further postulates that alleles in linkage disequilibrium with IL-1 alleles can be used to determine susceptibility to disease. Yet, the specification (page 66) states that "(t)he Mantel-Haenzel results summarized over the Leicester and Sheffield cohorts showed no significant differences in genotypic distributions at the IL-1A (-889), ILb (+3954), and ILb (-511) loci between restenosers and non-restenosers (Table II)". Accordingly, alleles which are considered to be in linkage disequilibrium with IL-1RN (VNTR) were found to show no correlation with restenosis. This finding also underlies the unpredictability in the art of cardiovascular disease diagnosis in that it clarifies that there is not a universal association between IL-1 alleles and the occurrence of restenosis and that it is highly unpredictable as which additional alleles, if any, could be used to determine susceptibility to restenosis. Additional evidence of the unpredictability in the art of establishing a correlation between IL-1 alleles and restenosis is found

in the specification which provides teachings which are directly contradictory to the findings set forth on pages 66 and 67 of the specification. In particular, page 88 of the specification states that "allele 2 of the 4845, -511, +3954 and VNTR markers in the IL-1RN gene will be over-represented in restenosis". Yet, claims 2 and 77-79 are drawn to methods in which the presence of **allele 1** of IL-1A (+4845), ILb (-511), ILb (+3954) and IL-1RN (+2018) are detected as indicative of the presence of or predisposition to restenosis. It is requested that Applicants provide an explanation regarding these conflicting teaches in the specification. The findings presented in parent application 09/431,352 further establish the unpredictability of using alleles in linkage disequilibrium as a means for diagnosing susceptibility to cardiovascular disease. For example, the '352 specification teaches that other alleles in the haplotype containing allele 2 of IL-1RN (VNTR), IL-1RN (+2018) and IL-1A (-511) are not correlated with single vessel coronary artery disease. The specification at page 83 states that "(t)here was no significant difference between the control and the diseased patients in the frequency of the different alleles in the genes for IL-1A (-889 marker), IL-IL-1B (+3954 marker), or TNFα (-308 marker)". Since even alleles in linkage disequilibrium with allele 2 of IL-1RN (VNTR), IL-1RN (+2018) and IL-1A (-511) are not correlated with single vessel coronary artery disease, there is no predictable means for determining which of the multitude of known and unknown alleles of IL-1 genes and other genes would be associated with a cardiovascular disease such as restenosis and additional alleles could only be identified by one of skill in the art through extensive trial and error experimentation. The specification at page 84 of '352 also teaches that ILb (-511) allele 2 is

present in 54% of patients with multiple coronary artery disease, versus 38% of control patients. The specification (page 85) further states that "(t)here was no significant difference between the control and diseased patients in the frequency of different alleles in the genes for IL-1A (-889 marker), ILb (+3954 marker), and IL-1RN (VNTR marker)". This result indicates that alleles characterized in the specification of '352 as being in linkage disequilibrium with ILb (-511) allele 2 are not in fact correlated with the occurrence of multiple coronary artery disease, thereby further establishing the unpredictability of using alleles in linkage disequilibrium with IL-1 alleles as diagnostic markers for cardiovascular disease. Moreover, it is noted that claims 1, 3, 4, 6 and 7 are broadly drawn to methods for detecting if a subject has or is predisposed to restenosis by detecting the presence of any restenosis associated allele. However, as discussed above, the specification has established only a correlation between specific IL-1RN (VNTR) allele 1 and the occurrence of restenosis in SVD patients. It is noted that the prior art of Bray et al (U.S. Patent No. 5,955,266) teaches the diagnosis of restenosis by detecting a specific polymorphism in the GPIIIa gene. However, the teachings in the art of an association between restenosis and one additional polymorphism in one gene does not provide specific guidance to enable the diagnosis of restenosis by detecting any polymorphism in any gene. It would clearly require extensive experimentation for one of skill in the art to analyze all other genes for the presence of any mutation or polymorphism correlated with restenosis, particularly given the high level of unpredictability in the art of establishing a correlation between an allele and the occurrence of disease and given the lack of sufficient guidance provided by the specification. Case law has

established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has identified only one allele , IL-1RN (VNTR) allele 1, which may be useful for diagnosing susceptibility to restenosis in SVD patients. Thereby, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of IL-1 genes and the entire genome for additional alleles which may show an association with restenosis. Again, the specification illustrates the unpredictability in establishing a correlation between an IL-1 alleles and the occurrence of cardiovascular disease in that the specification teaches that while one allele has been found to be correlated with restenosis, other alleles characterized as being in linkage disequilibrium with said allele are not correlated with restenosis. In addition, the specification clearly teaches that while one allele may be correlated with a particular type of cardiovascular disease, that same allele may not be correlated with a different type of cardiovascular disease. The specification has not provided any

specific data clearly establishing the occurrence of ILb (-511), ILb (+3954), ILb (+4845) alleles in restenosis and no working examples are provided in the specification in which these alleles have been successfully employed to determine the presence or predisposition to restenosis. Accordingly, in view of the lack of information in the specification as to how to reasonably identify other alleles correlated with restenosis without undue experimentation and in view of the unpredictability in the art in correlating the presence of an allele with a disease, particularly in correlating the presence of an IL-1 polymorphism with restenosis, the specification has not adequately taught one of skill in the art how to practice the claimed invention as it is broadly claimed.

6. Claims 1-7 and 77-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 and 77-79 are indefinite for failing to recite a final process step which agrees back with the preamble. The claims are drawn to methods for determining whether a subject is predisposed to developing an arterial restenosis. However, claims recite a final step in which the detection of an allele indicates that the subject has or is predisposed to restenosis. Therefore, it is not clear as to whether the claims are intended to be limited to methods for diagnosing arterial restenosis or methods for diagnosing restenosis.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 4, 6 and 7 are rejected under 35 U.S.C. 102(e) and 102(a) as being anticipated by Bray et al (U.S. Patent No. 5,955,266).

Bray (see claims 17 and 19) teaches methods for diagnosing a patients predisposition to restenosis wherein the method comprises isolating DNA from the patient, analyzing the DNA for the presence of a particular allele, comparing the patients allele with an allele which is known to be predictive of coronary artery disease, wherein the presence of an allele in the patient which is similar to the known allele is indicative of a predisposition to restenosis. In particular, Bray teaches that the target nucleic acid to be analyzed may first be amplified by PCR (claims 7 and 8) and that following amplification, the target nucleic acid is digested by a MspI restriction enzyme and size analysis is performed by electrophoresis of the digested amplification products (claims 13 and 18).

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.32 (c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 6 and 7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,268,142. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '142 are both inclusive of methods for determining a patient's predisposition to disease wherein the methods comprise detecting IL-1A (+4845), IL-1RN (+2018) or ILb (-511). It is noted that the claims of '142 are inclusive of methods for determining predisposition to any disease or condition associated with an IL-1 inflammatory haplotype, including cardiovascular disorders and thereby are inclusive of methods for detecting the cardiovascular disorder of arterial restenosis.

9. Claims 1-7 and 77-79 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No.6,210,877.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '877 are both inclusive of methods for determining a patient's predisposition to disease wherein the methods comprise detecting IL-1RN (VNTR) or ILb (-511). It is noted that the claims of '877 are inclusive of methods for determining predisposition to coronary artery disease and thereby are inclusive of methods for detecting the coronary artery disease of arterial restenosis.

10. Claims 1-7 and 77-79 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-4 and 6-13 of copending Application No. 09/431,352. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '352 are both inclusive of methods for determining a patient's predisposition to arterial restenosis wherein the methods comprise detecting IL-1A (+4845), ILb (+3954), IL-1RN (+2018) or ILb (-511). It is noted that the claims of '352 are inclusive of methods for determining predisposition to any cardiovascular disorder and thereby are inclusive of methods for detecting the cardiovascular disorder of arterial restenosis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

September 17, 2001

CARLA J. MYERS
PRIMARY EXAMINER